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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/313,434	05/17/1999	DANIEL K. PODOLSKY	00786/432001	3909

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EXAMINER
DUFFY, PATRICIA ANN

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 06/25/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/313,434	Podolsky
Examiner	**Art Unit**
Patricia A. Duffy	1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *1-30-02 and 2-15-02* .

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-12* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Response to Amendment

1. The amendment filed 1-30-02 has been entered into the record. Claims 1-12 are pending and under examination.

2. The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.

3. Any rejection not reiterated herein is withdrawn.

Rejections Maintained

4. Claims 1-12 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of enhancing corneal epithelial wound healing comprising contacting the cornea with intestinal trefoil factor (ITF) or enhancing fragment thereof in an amount sufficient to enhance corneal epithelial wound healing, it does not reasonably provide enablement for treatment of all eye disorders including keratitis (inflammation of the cornea of the eye) of any type or keratoconjunctivitis (the combined inflammation of the conjuctivia and cornea of the eye) of any type, ophthalmic herpes zoster, ocular inflammation, or scarring of the eye tissues (cicatricial penhigoid). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims is maintained for reasons made of record in the previous office action.

Applicants arguments have been carefully considered but are not fully persuasive. Applicants argue that the methods of the invention are directed to maintenance of epithelial viability and integrity. The claims are not so limited. The amendment to the independent claims does not cure this deficiency. The claims still encompass all means/methods of treatment and the effects are not related to corneal epithelial wound

healing. Applicants argue that the disorders can not be characterized as inflammatory disorders. This is not persuasive, the disorders have an inflammatory component and the claims as currently crafted specifically include treatment of this inflammatory component. The claims are not limited to treatment of corneal wounds by contacting with an amount effective to promote corneal epithelial growth/spreading/wound healing. The trefoil peptides have not been demonstrated to have the variety of effects that encompass treatment of the associated inflammation of the disorders listed in the claims. Applicants claims are not limited to promotion of migration of corneal epithelial cells across areas of damage (i.e. the instant corneal wound healing). Applicants have not limited to the treatment for which they are clearly enabled. Applicants which to claim all of the scope of treatment of these eye disorders that encompass such unpredictable areas of inflammation, for which neither ITF or hSP have predictable and reproducible effects. The effect on the inflammatory component of these diseases are not set forth in the specification and Applicants are not entitled to claims that encompass this unpredictable area. Clearly, the record establishes that inflammation is a component of the recited diseases characterized by epithelial injury, however applicants are not entitled to treatment of the inflammatory component and the claims still encompass this component. Applicants argue that the effect of epithelial restoration and corneal wound healing may be imputed to all trefoil peptide family members based on a combination of the data presented in the specification and in the prior art. This is not persuasive, in both the prior art and in the specification the art, the epithelial is directly contacted with specific trefoil factors. These claims do not require direct contacting with the trefoil factor, further, applicants family of working "trefoil factors" is limited to two specific factors, but the claims are drawn to any and all functional equivalents. The specification is not

enabling for all functional equivalents, because it fails to set forth a representative number of working embodiments for the world of "functional equivalents". There is no common core structure set forth in the claims that distinguishes members of the "trefoil family" from other proteins and the specification broadly defines such a family. As previously set forth similar structure does not predict similar function. Even given the known structures for ITP and SP, it is known for nucleic acids as well as proteins, for example, that even a single nucleotide or amino acid change or mutation can destroy the function of the biomolecule in many instances, albeit not in all cases. The effects of these changes are largely unpredictable as to which ones have a significant effect versus not. Therefore, the citation of sequence similarity or structural conformation results in an unpredictable and therefore unreliable correspondence between the claimed biomolecule and the indicated similar biomolecule of known function and therefore lacks support regarding enablement. Several publications document this unpredictability of the relationship between sequence and function, albeit that certain specific sequences may be found to be conserved over biomolecules of related function upon a significant amount of further research. See the following publications that support this unpredictability as well as noting certain conserved sequences in limited specific cases: Gerhold et al.[BioEssays, Volume 18, Number 12, pages 973-981{1996)]; Wells et al.[Journal of Leukocyte Biology, Volume 61, Number 5, pages 545-550 (1997)]; Russell et al.[Journal of Molecular Biology, Volume 244, pages 332-350 (1994)] and Attwood, [Science, 290:471-473, (29 October 2000)]. Applicants have not sufficiently characterized the properties of the family such that one skilled in the art could readily predict what function a particular protein will have based on its primary structure. Applicants specification fails to teach any effect of any disclosed trefoil protein on any inflammatory process such as scarring, mitogenesis,

production of secondary inflammatory mediators. The art specifically teaches that epithelial growth factor promotes corneal wound healing but at the cost of an inflammatory reaction (Burling et al, American Journal of Veterinary Research 61(9):1150-1155, 2000). Thus, growth factors that promote wound healing may also promote inflammation. Neither the art, nor the specification as originally filed provides a clear cut correlation of the enhancement activity of corneal wound healing by growth factors with the ability of the same to treat any eye disorder or ocular inflammation. Therefore, in the absence of teachings in the specification that trefoil proteins mitigate ocular inflammation caused by conjunctivitis, herpes zoster or any other mechanism, the treatment of eye disorders generic lesions (i.e. zoster lesions) or any inflammatory eye disorders is not enabled by this specification at the time of filing. Applicants arguments are in many cases not commensurate in scope with the claims. Applicants arguments are directed to corneal epithelial wound healing but the claims encompass more (i.e. inflammation, virus infection).

The rejection is maintained.

5. Claims 1-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims recite the phrase "treatment of an eye disorder characterized by an injury to the corneal epithelial" however the claims never recite what aspect of the disorder(s) are positively affected or mitigated. Applicants amendments do not obviate this rejection because the claims still do not indicate what aspects of the eye disorder are mitigated. As such, the metes and bounds of "treatment" can not be ascertained, applicants have only further characterized the type of eye disorder, not the effect of treatment.

6. Claims 1, 2, 6, 7, 8, and 12 stand rejected under 35 U.S.C. 102(b) as being clearly anticipated by Wilson, U.S. Patent No. 5,703,047 issued December 30 1997 is maintained for reasons previously made of record.

Applicants arguments have been carefully considered but are not persuasive. Applicants argue that the cited treatment proteins do not fall within the family of trefoil protein as defined in the specification and the examiner takes the specification out of context. This is not persuasive, Applicants own definition in the specification does not require the "family of trefoil proteins" to have all the relied upon characteristics. The specification specifically states "Members of the trefoil family of proteins typically will have at least one of the following properties in common: (I) common structural domain (e.g. the trefoil shaped secondary structure, (ii) a degree of amino acid or nucleotide sequence homology **or** [emphasis added] (iii) a common functional characteristic." The recited growth factors have a common functional characteristic and a degree of amino ac id or nucleotide sequence homology. Applicants argue that the proteins of the prior art do not have the trefoil structure but presents no factual evidence therefore. Further, even if the therapeutic proteins of the prior art did not have the trefoil structure, they still meet characteristics (ii) and (iii) of the definition in the specification. The definition in the specification does not require that all family members have the trefoil structure as asserted by Applicants. Applicants own specification does not say that the family **must** have all the characteristics in common. The fact that a few of the peptides of the specification do in fact possess a trefoil structure, does not abrogate applicants own words that indicate that the trefoil family of proteins are not required to have such.

The rejection is maintained.

Status of Claims

7. All claims stand rejected.

Conclusion

8. **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

9. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy, Ph.D. whose telephone number is (703) 305-7555. The examiner can normally be reached on Monday-Thursday and Saturday from 10:30 AM to 7:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached at (703) 308-3909.

Patricia A. Duffy, Ph.D.
June 24, 2002

Patricia A. Duffy, Ph.D.
Primary Examiner
Group 1600